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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/010,114

Filing Date: November 13, 2001

Appellant(s): BOUTIN, RAYMOND H.

Cathy Kodroff
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 17, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(2) Related Appeals and Interferences

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A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct. For clarification, the examiner would like to point out that claim 3 was subject to a restriction/election requirement. The remaining claims were all linking claims. Applicant later amended claim 3 to remove the elected subject matter, which resulted in claim 3 being withdrawn from consideration. The elected subject matter in claim 3 was refiled as independent claim 49.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

The rejection of claims 1-3, 5-9 and 17-52 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) *ClaimsAppealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Art of Record*

Blau et al. Molecular Medicine: Gene Therapy - A Novel Form of Drug Delivery. The New England Journal of Medicine. November 2, 1995, pp. 1204-1207.

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- Mulligan, R. The Basic Science of Gene Therapy. *Science*. May 1993, Vol. 260, pp. 926-932.
- Gene Therapy's Growing Pains. *Science*. Vol. 269, 25 August 1995, pp. 1050-055.
- Anderson, W.F. Gene Therapy. *Scientific American*. September 1995, pp. 124-128.
- Russell, S.J. Replicating Vectors for Gene Therapy of Cancer: Risks, Limitations and Prospects. *European J. Cancer*. 1994, Vol. 30A, pages 1165-1171.
- Gutierrez et al (1992) *The Lancet*, Vol. 339, page 720
- Treco et al. Non-Viral Gene Therapy. *Molecular Medicine Today*. 1995, Vol. 1, pp. 314-321.

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-9 and 17-52 remain rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for methods for the transfer of a nucleic acid composition to cells in culture comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety, does not reasonably provide enablement to methods for the nuclear transfer of a nucleic acid composition to cells in vivo comprising introducing a multifunctional molecular complex to cells where the complex comprises a nucleic acid encoding a therapeutic protein or polypeptide and a transfer moiety for reasons set forth in the office actions mailed December 8, 2003 and September 22, 2004, and repeated here in their entirety.

NATURE OF THE INVENTION

The invention is to the delivery of nucleic acid sequences encoding a therapeutic protein by complexing the nucleic acid to the multifunctional complexes as claimed. The claims are enabled for methods of transfer where the target cells are cultured cells.

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However, when the claims are read in light of the specification, the claimed methods disclosed to be to methods of in vitro, cell culture, and in vivo delivery for the treatment of disease. The claims are not enabled for the latter embodiment. The in vivo aspect of claims 1, 2, 5-9 and 17-52 is interpreted as gene therapy as the specification does not disclose a use for delivering a therapeutic protein other than for therapeutic purposes (see specification, page 3, lines 9-13; page 39, lines 15-19 and 24-32; and page 40, line 34 to page 41, line 2). As applicant has broadly disclosed treatment of any disease and emphasized hyperproliferative diseases, but stated no specific diseases, the examiner believes that the general teachings in the art of gene therapy and cancer gene therapy at the time of filing are appropriate in summarizing the state of the art at the time of effective filing date, September 28, 1994.

STATUS OF THE ART AT THE TIME OF FILING

The art taught, at the time of filing, that gene therapy was unpredictable without guidance being given for achieving effective treatment. In particular, articles summarizing the state of gene therapy stated expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome (Blau (1995), page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Mulligan stated that gene therapy is unpredictable and cautioned that "a number of key technical issues need to be resolved before gene therapy can be safely and effectively applied in the clinic" (Mulligan (1993), pages 926-932, see Abstract). Science News Report states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models (Science (1995) 269, page 1050, col. 2, parag. 1, lines 6-15). Further, the reports stated that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (Science 269, p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging

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problem for the entire field" (Science 269, p. 1054, col. 3). James Wilson, one skilled in the art, stated that " '{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (Science 269, p. 1055, col. 2). Anderson, in a review of gene therapy for genetic diseases, states that continued expression is necessary, and that vectors for gene therapy are hit or miss because many viral promoters are shut off in primary cells *in vivo* (Anderson (1994), page 281, col. 2, parag. 1). Thus gene therapy in general was regarded as unpredictable by the art at the time filing, and this unpredictability laid in the realm of expression and delivery of the gene.

As for cancer as a representative hyperproliferative disease, the unpredictability for the same reasons, expression and delivery of the gene of interest for therapeutic effect, was acknowledged by the art. Russell stated that gene delivery to tumors cell *in vivo* by direct injection of a plasmid or virus achieves a relatively low efficiency of gene delivery as the plasmid or virus can not permeate the tumor (Russell (1994), page 1165, col. 2, parag. 4, lines 3-7). Russell also states that it is improbable that plasmids or viruses would be efficiently delivered to tumors if administered intravenously (Russell (1994), page 1166, col. 1, lines 3-11). Russell states that replicating viral vectors may offer the best chance of delivering sufficient gene to tumors for effective treatment. However, Russell also states that research of replicating viruses is needed for the delivery of therapeutic genes to tumors *in vivo* (Russell (1994), page 1167, col. 2, parag. 1-5). Furthermore, Gutierrez et al. (1992) reviews this technology, and indicates at pages 716-717 that there are two major limitations to mammalian cell transfection. The first is a much lower efficiency of gene expression in comparison with prokaryotic systems, with considerable differences between eukaryotic cell lines. Unlike rodent cells, most primate and human cells can integrate only a small amount of foreign DNA (about 6 kilobases); as a result, only about 10-30% of clones selected for the expression of one transcription unit will also contain a second unit in intact

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form. The second problem is the short-lived response after successful transfection (a few months at most) regardless of the method used. We know very little about the processing steps within the cell. Clearly, there are problems of degradation by extracellular nucleases, absorption onto and uptake into cells, transport from cytoplasm to nucleus integration into host chromosomes, mutation, the expression of non-integrated DNA, and the transcriptional control of the transgene. Gutierrez et al also stated that for somatic cell replacement therapy, many technical hurdles need to be overcome and that suitable controls for expression vectors were not known and thus the replacement gene therapy would not have direct consequences on tumors for some time (Gutierrez (1992), page 720, col. 1, parag. 1 and parag. 3, lines 1-4). Thus a specific embodiment disclosed for a method of in vivo delivery to treat a disease such as cancer was not regarded as enabled at the time of filing.

In as much as applicant's claims are directed to the use of non-viral means, cationic lipid accompanied by receptor mediated endocytosis means, for introducing DNA into a cell in vivo for therapeutic purposes. However, at the time of filing Treco (1995) stated, with regards to receptor mediated uptake of DNA for therapy that the method has promise but there are several major issues to be resolved: undesirable uptake of DNA by non-target cells and non-specific uptake are the most relevant to present claims (page 318, col. 2, parag. 2, lines 1-6). Treco clearly indicates that while non-viral means for gene therapy were being developed at the time of filing, none had been shown to effectively overcome the lack of delivery and expression that plagued the field at that time. Thus, non-viral delivery of genes was not regarded as enabled by the art at the time of filing.

GUIDANCE AND WORKING EXAMPLES

The specification discloses the treatment of any disease or condition, and specifically discloses cancer and psoriasis as particular hyperproliferative diseases (specification, pages 47 and 48). Thus, this disclosure is not on point for the particular invention examined in this

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prosecution. However, the specification fails to disclose any particular DNA sequences that can be administered by applicant's claimed methods to treat these or any other diseases. There is no guidance on DNA sequences to treat cancer, a multifocal disease, or psoriasis. The specific examples provide no additional guidance. Example 11 teaches the expression of lacZ when a plasmid comprising a β-galactosidase gene complexed to a transfer moiety of the invention is injected into mouse thigh muscle (page 77). Example 12 teaches the finding of hepatitis B surface antigen in the blood mice injected i.v. with a multifunctional molecular complex comprising a plasmid containing a hepatitis B virus surface antigen gene complexed to a transfer moiety of the invention (pages 77-78). However, in neither case does the expression of the delivered gene result in an alleviation of a symptom of any disease, hyperproliferative disease, cancer or psoriasis. The data presented do not overcome the lack of enablement established for the claimed invention at the time of filing. Thus, the skilled artisan, at the time of filing, would have needed to engage in an undue amount of experimentation without a predictable degree of success to make and use the invention as claimed.

(11) Response to Argument

Applicant argues that the examiner has incorrectly rejected the claims under 35 U.S.C. § 112, first paragraph (Brief, page 3, parag. 1). Applicant argues that the examiner is requiring applicant to demonstrate that a protein encoding by the nucleic acid molecule delivered by a multifunctional complex according to the method of the invention confer a specific therapeutic benefit or other physiologic effect (Brief, page 4, lines 1-4). Applicant argues the examiner has failed to establish a reasonable basis to question the enablement of claims which recite a method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex in to cells in vivo. Further, applicant argues the claims do not recite "in vivo" (Brief, page 4, parag. 2).

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Applicant argues they only need to enable one skill in the art to make and use the claimed invention, which comprises a nucleic acid composition, without undue experimentation (Brief, page 4, parag. 3). Applicant argues that since the claims do not require a therapeutic effect, a demonstration of such is not needed (Brief, page 4, parag. 3).

These arguments are not persuasive.

Applicant responded to a restriction/election requirement, filed September 11, 2003, by electing group I, a method for the transfer of a nucleic acid composition to cells where the nucleic acid encoded a therapeutic agent. Based on this election, claims 1-9 and 17-48, of record at that time and later through amendments, claims 1,2 4-9, 17-52, are interpreted as methods of delivering a therapeutic agent using applicant's novel multifunctional molecular complex. When the claims are read in light of the specification, the only use disclosed for in vivo delivery is to for therapeutic purposes (see specification, page 3, lines 9-13; page 39, lines 15-19 and 24-32; and page 40, line 34 to page 41, line 2). Further, when the claims are read in light of the specification, it is clear that the scope of "cell" encompasses both cells in an animal, patient or subject, and cells in culture. Thus, while the specification enables delivery and expression in cells in culture or cells in vitro, the method of delivering has no enabled use for delivery to cells in an animal, patient or subject, that is cells in vivo. There is no evidence that the method results in sufficient delivery of a nucleic acid in vivo to offer a therapeutic effect. The specification offers no use for mere delivery of a therapeutic agent in vivo absent a therapeutic effect. The specification broadly discloses treatment of any disease and emphasized hyperproliferative diseases, such as cancer and psoriasis (page 47, lines 16-22). As the claims are directed to a broad category of therapeutic agents, and the specification is broad in the disclosure of diseases in general, general teachings in the art of gene therapy and cancer gene therapy at the time of filing

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are appropriate in summarizing the state of the art at the time of effective filing date, September 28, 1994.

Applicant argues that the articles cited by the examiner describe problems associated with viral-based delivery vehicles and plasmid-based delivery vehicles (Brief, page 5, parag. 1). Applicant argues that these are not pertinent to the invention as the invention does not rely on these types of vehicles for delivery (Brief, page 5, parag. 2). Applicant argues that Treco's receptor mediated delivery of DNA sequences is also not relevant to their invention (Brief, page 5, parag. 3). Applicant argues that Treco discusses advantages of DNA-lipid complexes (Brief, page 5, parag. 3). Applicant argues that the examiner has not countered the statements in Treco (Brief, page 5, parag. 3). Applicant argues their invention is more analogous to DNA-lipid delivery than the DNA-protein complex of Treco (Brief, page 6, lines 1-2). Applicant argues that the examiner has not offered any scientific support for the position that transcription and translation of a protein would be different in cell cultures than in vivo once the cell membrane has been penetrated (Brief, page 6, parag. 2). These arguments are not persuasive.

Each of Blau, Science News Reports, Miller and Gutierrez discuss the failure of gene therapy protocols they are relevant in providing a general background to the state of gene therapy at the time of filing. In each instance, extensive prior research was conducted on the particular vectors described in these references, research which included in vitro expression. Further, the references are relevant because they address liposomal delivery and adenoviral delivery. Applicant states that their invention is mostly like liposomal delivery, but this is not accurate. The claims require an endosomal membrane disruption component, a class that encompasses adenoviruses. Science – News Report (SNR) addresses applicant's arguments. It is important to realize that the effective filing date of the present case is 1994, which is the date for enablement of the claims on appeal. SNR

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states that "gene therapists are still encountering difficulties in transfer genes to adequate numbers of target cells and getting them expressed" (page 1050, col. 1-2, bridg. sentence). The reference states that nearly all the gene therapy trials approved at the publication date of 1995 have been for phase I trials, which addresses safety, not efficacy (page 1055, col. 2, parag. 1, lines 1-3). The report quotes a skilled artisan, Nelson Wivel, as saying that phase I trials can be judged on effectiveness (page 1050, col. 2, parag. 1, lines 4-5). Thus, it does not matter if cell culture data is successful or not, gene therapy at the time of filing was not regarded as successful. SNR states that liposomes, which applicant has indicated is more relevant to their invention, has low efficiency of gene transfer (page 1053, Table "vectors in RAC-approved clinical trials." SNR states that adenoviruses have a great drawback in that they induce immune responses which cannot be overcome by administering large amounts of adenoviral vectors or replication defective adenovirus because the immune system neutralizes the vectors prior to a therapeutic effect (page 1052, The Trouble with Vectors, col. 2, parag. 2, lines 1-5). Gutierrez states, with regard to applicant's specific embodiment of cancer, "a cell line can be transfected quite readily in vitro but to this for a solid tumor in vivo is less easy" (Gutierrez, page 716, col. 2, parag. 3, lines 1-2). Further, while Treco speaks admirably of liposomes, and indicates that their use in vivo has caused longer expression in several target tissues, there is no indication in Treco that the longer expression resulted in a therapeutic benefit (Treco, page 319). The art is clear that in a general and specific way that gene therapy was unpredictable, as determined by the skilled artisan at the time of filing. Further, vectors that are like in some ways to applicant's multifunctional molecular complexes, were also regarding as not being effective in gene therapy protocols. This, and the lack of correlation between in vitro expression and a therapeutic effect, renders applicant's invention as lacking enablement at the time of filing.

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Applicant argues that in a Declaration filed November 24, 1998, evidence is provided of an immune response generated against HSV gD using the claimed method (Brief, page 7, parag. 4). Applicant argues that parag. 11-15 of the declaration demonstrated the *in vivo* expression of the nucleic acid encoding the gD protein following intramuscular injection into mice ((Brief, pages 7-8). Applicant argues that a cellular and humoral immune response was obtained (Brief, page 8, lines 1-6). Applicant argues that the examiner has not provided evidence that a cell can determine the difference between delivery of encoded therapeutic proteins and encoded immunogenic protein (Brief, page 8, parag. 3). Applicant argues that the declaration also provided evidence that the multifunctional complex can deliver nucleic acid to multiple cell types (Brief, page 9, parag. 1). Applicant argues that more than one multifunctional complex was used in the studies (Brief, page 9, parag. 2). This argument is not persuasive.

The declaration demonstrates a humoral and CTL response to a multifunctional molecular complex comprising a nucleic acid encoding HSV gD. This protein is not a therapeutic protein, it is an immunogen, that is it would be indicative of protection against HSV infection. This invention is in nonelected group II of the restriction/election requirement mailed August 13, 2003. The declaration at paragraphs 10-14 thus are directed to vaccine methods. The declaration at paragraphs 7-10 are to direct to *in vitro* cell delivery. The evidence provided in the declaration is directed to vaccination against a pathogen which is not examined in this prosecution.

A cell, of course, cannot determine if a nucleic acid encodes a therapeutic agent or a pathogen for a vaccine purposes. However, in the treatment of established diseases more is needed than making a protective immune response. What is required that sufficient of the therapeutic protein be produced to alleviate a symptom associated with an established disease. For example, if cancer or psoriasis were to be treated a DNA sequence would need

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to be delivered that when expressed alleviated some symptom of these diseases. The specification provides no such correlation between the method of delivery and any relief from symptoms. In fact the specification provides no guidance on DNA sequences encoding therapeutic agents to be delivered to treat any disease, hyperproliferative disease, cancer or psoriasis. Thus, the artisan would not know what DNA sequences to deliver in addition to not having a predictable degree of success without undue experimentation in obtaining sufficient expression to alleviate a symptom of any disease.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

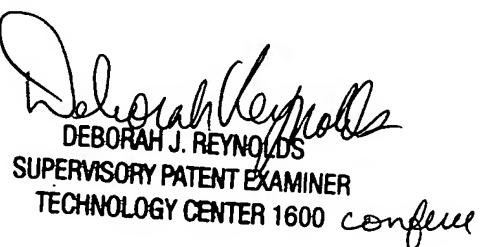
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